Chapter (10)

Rheumatic fever and Rheumatic Heart Disease

CARDIO-NOTES

Part III: Management of Chronic Cardiac Cases

(An ESC and ACC/AHA guidelines based approach)

Ahmed Abdelmageed Alfarra, MSc

National Heart Institute

Cairo, Jan 2024

This chapter will be published in the upcoming **part III** of ***CARDIO-NOTES*** series

Part I: Cardiac Emergencies (ESC and ACC guidelines based step-by-step approach), published, 2023

Part II: CVS Drugs (the clinical use of CV drugs), published, 2023.

Part III: Management of Chronic Cardiac Cases (an ESC and ACC/AHA guidelines based approach), still under final revision for publishing

Rheumatic fever and Rheumatic Heart Disease

Introduction

Rheumatic fever is a multisystem autoimmune inflammatory disease that is triggered by infection with group A streptococcus (GAS). It is a disease of overcrowding and bad immune response.

- Rheumatic fever (RF) may present in acute stage (acute rheumatic fever) or in chronic stage (chronic rheumatic heart disease), acute rheumatic fever (ARF) may resolve completely or progress to chronic stage.
- Repeated or severe episode of ARF leads to chronic rheumatic heart disease (RHD), more than half of those with ARF progress to RHD within 10 years of their initial episode and more than one-third of those people develop severe RHD, for this reason we need to give secondary prophylaxis (to decrease ARF recurrence → decrease progression).
- Peak prevalence of ARF is between 5-14 years and peak prevalence for RHD between 35-44 years.
- About 3% of untreated acute streptococcal sore throat were followed by acute rheumatic fever and about 10-40% (30%) of sore throat and all cases of tonsillitis are caused by GAS. Skin strept infection (impetigo) is also associated with development of ARF.
- Appropriate antibiotic therapy for GAS infection will prevent ARF in most cases (not all cases); in up to two-thirds.
- Asymptomatic GAS infection can trigger ARF and recurrent ARF can occur in the setting of adequate GAS treatment.
- About 1/3 of ARF cases are not preceded with clinical GAS infection, and about 50-70 of RHD are not preceded by ARF (only about 30-50% of RHD are preceded by ARF).
- Chronic RHD evolves over years after the first episode of ARF (borderline echocardiographic findings suggestive of RHD >>> subclinical RHD {no murmur} >>> clinical RHD {with murmur} >>> symptomatic RHD).

Prevalence of RHD in Egypt is about 1-3% (10-30/1000) of school aged children

Criteria for diagnosis of acute rheumatic fever, Revised Jones Criteria 2015

	High risk population (as Egypt)*	Low risk population**
Definite ARF (initial)	2 major criteria + evidence of GAS infection. 1 major + 2 minor criteria + evidence of GAS infection.	
Definite ARF (recurrent, after > 90 days)	2 major criteria + evidence of GAS infection. 1 major + 2 minor criteria + evidence of GAS infection. 3 minors criteria + evidence of GAS infection	
Likely ARF (the most likely diagnosis)	Patient has 1 major & 1 minor criteria, or patient who has no evidence of GAS infection. Then those are further categorized according to level of confidence in diagnosis into probable (highly suspected) or possible (uncertain/just a clinical suspicion). In another words <u>probable</u>: 1 major + 1 minor or 2 minors with inclusion of evidence of preceding GAS infection as a minor criteria, <u>possible</u>: doesn't met definite or probable criteria	

Major criteria	• **Carditis** including subclinical carditis (chronic carditis may be the only manifestation of RF at time of its presentation) • Polyarthritis or **monoarthritis or polyarthralgia** (migratory, asymmetrical, large joints). • **Sydenham chorea** (may be the only manifestation of ARF at time of its presentation) • **Erythema marginatum** (almost never occur as the sole major manifestation) • **Subcutaneous nodules** (almost never occur as the sole major manifestation)	• **Carditis** (including subclinical carditis) • **Polyarthritis** only • **Sydenham chorea** • **Erythema marginatum** • **Subcutaneous nodules** **Polyarthralgia or monoarthritis** are majors in high risk and minors in low risk population
Minor criteria	• Fever ≥ 38 • Monoarthralgia • ESR ≥ 30 mm/h • CRP ≥ 3 mg /dl • Prolonged PR interval on ECG	• Fever ≥ 38 .5 • **Polyarthralgia or monoarthritis** • ESR ≥ 60 mm/h • CRP ≥ 3 mg /dl • Prolonged PR interval

* Living in community with low rate of ARF (> 2/100,000 per year in 5-14 year-old) or RHD > 1/1000 per year at any age.
** Living in community with low rate of ARF (≤ 2/100,000 per year in 5-14 year-old) or RHD ≤ 1/1000 per year at any age.

- Evidence of GAS infection = throat culture or ASOT or RADT.
- If polyarthritis is considered a major criterion, don't count arthralgia or monoarthritis as an additional minor criteria.
- If carditis is present, don't consider prolonged P-R interval as additional minor criterion.
- If there is established RHD, recurrent attacks diagnosed by 2 minor criteria + evidence of GAS infection (WHO).
- Indolent carditis: sub-acute illness develops over several weeks or months with severe cardiac involvement and little or no joint symptoms, usually have modest elevation of inflammatory marker and evidence of gas infection isn't required.
- Some patients present with arthritis not typical for ARF but with evidence of GAS infection and are said to have **poststreptococcal reactive arthritis** (in these cases arthritis may affect small joints and less likely to respond to anti-inflammatory and patient are considered not at risk of carditis and need no 2ry prophylaxis) but this diagnosis should rarely, if ever, be made in high risk population and antibiotic prophylaxis should be considered for at least 5 years as some patients developed later episodes of ARF indicating that initial diagnosis was atypical ARF.

- Echo with Doppler is recommended for all suspected or confirmed cases of ARF (class 1).
- Consider serial echo in any patient with suspected or confirmed ARF even in absence of carditis (class 2a).
- You may repeat echo within one month if the initial echo wasn't clear, or showed severe carditis or pericardial effusion.

- Patient presenting with monoarthritis should be considered to have septic arthritis until prove otherwise, and patient presenting with polyarthritis or polyarthralgia should be investigated for alternative diagnoses.
- ASOT usually rises within 1-2 weeks of infection and reach peak within 3-6 weeks, then start to decrease within 6-8 weeks and may remain elevated for months after GAS infection and reach to pre-infection level within 6-12 months. Single titer is usually misleading, and ideally sequential samples are more accurately define occurrence and time of infection, take one sample in acute phase then in the convalescent phase (2-4 weeks later) with positive test defined as rising of twofold or more, but if only a single sample is available, a titer exceeding the upper limit of normal is considered an evidence of preceding GAS infection.

In ARF: you may measure inflammatory markers (ESR, CRP) once weekly until become normal for one month.

- The antibody titer varies with age and geographic location, ideally should be determined for each geographic location. The upper limit of normal ASOT in normal Egyptian children is high; up to 400 IU/ml. ASOT upper limit of normal in New Zealand used for diagnosis of ARF is ≥ 480 IU/ml for children < 15 years. If the test is below upper limit of normal, it should be repeated 10-14 days (four-fold rise or fall is diagnostic). The recommended levels in Australia are as the following:

Age (year)	1-4	5-14	15-24	25-34	≥ 35
ASOT (IU/ml)	170	276	238	177	127

Primary prevention of RHD

The aim is to promptly diagnose and treat GAS infection for prevention of initial attacks of ARF/RHD.

- Use of penicillin prevents primary attacks of RF even when started as long as 9 days after onset of acute illness.
- Full course of an antibiotic is recommended even if the patient becomes asymptomatic few days after starting therapy.
- Nearly all GAS are susceptible to penicillin and beta lactams.
- The following are the drugs and doses that can be used in 1ry or 2ry prevention:

Drug	Dose for 1ry prevention	Dose for 2ry prevention
Phenoxymethyl-penicillin (penicillin V)	250 mg (15 mg/kg) 2-3 times daily if BW < 27 kg and 500 mg 2-3 times daily if BW > 27 kg for 10 days.	250 mg twice daily orally.
Amoxicillin	50 mg/kg/d once daily or in 3 doses, maximum 1 g/d for 10 days.	-
Benzathine benzylpenicillin G (BPG)	600,000 IU if < 20* kg and 1,200,000 IU if BW ≥ 20 kg, single IM dose in acute infection	600,000 IU if < 20* kg and 1,200,000 IU if BW ≥ 20 kg every 2-4 weeks, IM.

Cephalexin	500 mg (25 mg/kg) up 1000 mg twice daily for 10 days.	-
Azithromycin	12 mg/kg/d maximum 500 mg once daily for 5 days.	250 mg once daily orally.
Erythromycin	40 mg /kg/d or 500 mg twice daily for 10 days.	250 mg twice daily orally
Cotrimoxazole (Septin) for skin sores	4 mg/kg/dose for trimethoprim component (40 mg/5 ml syrup preparation), for adult 1 tab Spetrin DS twice daily for 3 days.	-
< 20 kg in Australian, < 30 kg in WHO and New Zeeland and < 27 kg in American guidelines.		

Treatment of acute rheumatic fever:

Anti-inflammatory/analgesic:

- **Ibuprofen**: 200-400 mg 3 times daily up to 2400 mg daily (5-10 mg/kg 3 times daily).
- **Aspirin**: 50-60 mg /kg/d in 4-5 doses (maximum 100 mg/kg/d, 4-8 g/d).

Treatment of carditis (valvulitis):

- Treatment of HF symptoms (anti-failure medications and valve surgery if indicated).
- **Prednisolone** (1-2 mg/kg/d, maximum: 80 mg/d) in patient with severe carditis and acute HF, and stop aspirin or other NSAID until discontinuation of steroid which stopped (gradually) after improvement of inflammatory markers and HF symptoms.

Treatment of chorea (by neurologist):

- **Carbamazepine**: 3.5-10 mg/kg orally twice daily.
- **Sodium valproate**: 7.5-10 mg/kg orally twice daily.
- **Prednisolone:** 1-2 mg/kg/d, is used only in severe chorea.
- Other advanced therapies include IVIG, and plasmapheresis.

Secondary prevention of RF/RHD

The aim is to prevent recurrent ARF and so progression of RHD

- Risk of recurrence of RF is low after age of 25 and is extremely low after age of 40 years.
- Risk of recurrence of ARF decreases once patient received 40% of BPG doses and after that there is 17% more reduction in risk for every 10% increase in adherence.
- BPG is more effective than oral penicillins.
- Deep intramuscular (IM) BPG is given every 4 weeks but in high risk group or patient with recurrent ARF despite 4-weeks regimen it is preferred to be given every 3 weeks or 2 weeks (2-weeks regimen is more effective than 3-weeks regimen which is more effective than 4-weeks regimen).

Using of SAP may reduce attacks of RF following GAS infection by about 80%

- BPG can be reconstructed with 1-2% lidocaine to relief injection site pain with no loss of efficacy.
- In case of uncertainty about diagnosis (possible RF), give BPG for 12 months then reevaluate the patient with clinical assessment and Echocardiography (class 2a).
- If the patient who is on 2ry prophylaxis showed recurrent symptoms (e.g; joint pain) but lack evidence of infection and normal echo, you may consider discontinuation of prophylaxis (class 2a).
- If the patient who is on 2ry prophylaxis showed sore throat or skin sore and BPG dose was given > 7 days ago, give additional antibiotic dose as for active infection (BPG level decreases to prophylactic level after 7 days).
- Perform penicillin sensitivity test before administration, every time.
- Benzathine Penicillin severe reactions are very rare, allergenic reaction is about 3.2% but severe anaphylaxis is about 0.2% and fatal reactions are exceptionally rare. If a rheumatic patient experienced true penicillin allergic reaction then he should be referred to immunologist to verify the type and severity of reactions and determine if there is absolute contraindication to penicillin.

BPG preparation for injection: dilute the vial in 3 ml sterile water or 1-2% lidocaine and shake vigorously.

Penicillin sensitivity test: Draw out 0.1 ml of diluted drug then further dilute with 1 ml sterile water then inject 0.1 ml (10 شرطات في سرنجة الانسولين ال100) subcutaneously in the forearm then circle this area and wait for 15 min to look for itching, swelling or any unusual symptoms. In case of doubt, repeat on the other arm with double strength test dose

Immediate True reactions (within 15 min- 2 hr)	**Delayed true reactions (within 5-15 days)**
Felling of fainting, itching, rashes, swelling and respiratory distress.	Rash, fever, joint pain.
Management: **for mild reactions**: reassurance, hydrocortisone (100 mg Solu-Cortef), antihistamine (avil). In case of **anaphylactic shock/ severe reactions** consider adrenaline (IM), fluids and oxygen ± CPR.	

Duration of secondary antibiotic prophylaxis (SAP)

Duration according to Australian guidelines (2022)				
Diagnosis	**Definition**	**Minimum duration of prophylaxis**	**Features to stop**	**Timing of ECHO after cessation**
Possible ARF (uncertain), no cardiac involvement	Incomplete features of ARF with normal ECHO & ECG	12 months (then reassess). For 5 years in NZ guidelines with regular review	No S/S of ARF, Normal echo or still uncertain (if probable or definite >> continue therapy)	At 1 year
Probable ARF	Highly suspected ARF	5 years or until age of 21 (whichever is longer),	No S/S of ARF within the previous 5 years,	At 1, 3, 5 years

	with normal ECHO	count from the most recent episode	Normal echo	
Definite ARF (with no cardiac involvement)	ARF with normal ECHO and ECG throughout the episode	5 years or until age of 21 (whichever is longer) لو أقل من 16 سنة يبقى لغاية عمر 21 سنة ولو أكبر من 16 سنة يبقى لمدة 5 سنين	No S/S of ARF within the previous 5 years, Normal echo	At 1, 3, 5 years
Definite ARF (with cardiac involvement)	ARF with carditis or RHD on ECHO or AV conduction abnormalities on ECG.	Most cases of RHD lack a history of past ARF. Further classified as the following:		
Borderline RHD (≤ 20 years) ***Stage A***	Borderline RHD on ECHO without history of ARF	Minimum for 2 years then reassess, if still borderline, continue for further 2 years and reassess	No ARF in the previous 2 years. Normalization of echo after 2 years of follow up	After 1-2 years of diagnosis and -2 years of stopping prophylaxis
Mild RHD ***Stage B***	Mild stenosis or regurgitation of a single valve or AV conduction abnormalities on ECG during ARF.	10 years or until age of 21 years in case of documented history of ARF (whichever is longer) or 5 years or until age of 21 years if no history of ARF (whichever is longer) لو أقل من 11 سنة يبقى لغاية عمر 21 سنة ولو أكبر من 11 سنة يبقى لمدة 10 سنين	Stable echo features for 2 years, no evidence of progression of RHD or no ARF in the previous 10 years	At 1, 3, 5 years
Moderate RHD ***Stage C or D***	Moderate regurgitation or stenosis of a single valve or combined mild regurgitation and/or stenosis of one or more valve.	10 years or until age of 35 years in case of documented history of ARF (whichever is longer) or 5 years or until age of 35 years if no history of ARF (whichever is longer). For 10 years or till age of 30 in NZ guidelines then review risk of GAS exposure; if high continue prophylaxis.	Stable echo features for 2 years, no probable or definite ARF within the previous 10 years	Every 12 months
Severe RHD	Severe stenosis or regurgitation of a single	10 years or until age of 40 years in case of documented history of	Stable echo features for 3 years,	Every 6 months

Stage C or D	valve, or combined moderate regurgitation and/or stenosis of one or more valve, or impending or previous valve intervention	ARF (whichever is longer) or 5 years or until age of 40 years if no history of ARF (whichever is longer), or lifelong if surgery indicated or causing HF	Patient or family preference to cease.	

Duration according to American guidelines (2009)	
RF without carditis	For 5 years or until age of 21 years whichever is longer.
RF with carditis but no residual lesion	For 10 years or until age of 21 years whichever is longer.
RF with carditis with residual lesion	For 10 years or until age of 40 years whichever is longer.
Duration according to New Zealand (NZ) guidelines (2014)	
No or mild RHD	For 10 years or until age of 21 years whichever is longer.
Moderate RHD	Until age of 30 then reassess.
Severe RHD	Until age of 40 then reassess but review at age of 30 years.
Duration according to WHO guidelines (2004) and Indian guidelines (2015)	
RF without carditis	For 5 years or until age of 18 years whichever is longer.
RF carditis	For 10 years or until age of 25 years whichever is longer.
Severe RHD	For life or up to 40 years of age.

- Echo may be more frequent based on clinical status.
- Normal ECG = no AV conduction abnormalities.
- Normal echo = see below.
- No prophylaxis is needed for patient older than 35 years diagnosed with mild or moderate RHD without evidence of ARF (older than 40 years with severe RHD, prophylaxis determined by specialist).
- Despite ARF recurrence is rare in older than 40 years, lifelong prophylaxis is recommended if patient has had or likely to need valve surgery.
- Some cases, rarely, may improve on echo, if moderate or severe cases improved, follow recommendations of the new status. Mild RHD may resolve over 10 years with appropriate prophylaxis.
- Endocarditis prophylaxis before dental procedure is recommended in patient with RHD in Australian and NZ guidelines but not in American guidelines.
- Dental review is recommended in all patients with RHD every 6-12 mo (also recommended by ESC 2023 IE guidelines).

Follow up of patients on SAP and monitoring of medication adherence

We measure BPG adherence by measuring the percentage delivered annually.

Percentage delivered (%) = number of doses administered divided by number of doses recommended multiplied in 100. Increased percentage delivered means increased adherence.

This method is simple and easy but accurate as it doesn't take in account the dose timing; patient may show 100% delivery percentage but some doses may be delivered at shorter intervals and other at longer intervals with substantial breaks in between.

So the second method is more accurate and predictive of ARF recurrence which will estimate the **days-at-risk of recurrent exposure**, the days that should be covered by BPG but actually missed, it is calculated from first day of the next BPG dose that is not delivered and this is determined according to the selected regimen, for example if you decide to give BPG every 3 weeks, and it is given on day 1 then the next BPG dose is due on day 22 and if this next dose is given later than day 22, then the first day at risk is day 22 and all subsequent days before administration. We calculate this days through calculation of the proportion of days covered (PDC) by dividing the days actually covered by BPG by the total numbers of days from the first dose, the ideal result should be 1 but if 0.8 or more then it is accepted.

Measures to decrease injection site pain with BPG:

- Firm pressure at site of injection for 10 seconds immediately before injection.
- Refrigeration of the needle before injection.
- Ice pack applied to the site before injection.
- Use any distracting stimuli to the skin.
- Use lidocaine with BPG (for dilution, 1ml of 1% preparation).
- Use anesthetic spray before injection (not so effective).
- Deliver injection very slowly (over 2-3 min).
- Use analgesic (paracetamol) if needed after injection.
- Use sedative if needed during injection procedure.

Echo features of RHD according to 2023 World Heart Federation (WHF) guidelines

Screening criteria

It is designed to be used by non-expert for detection of suspected cases of RHD in settings of high provenance and limited resources, this is applicable for individuals aged 20 years or less, for that you may use hand-held machine (doesn't rely on spectral Doppler measurments for simplification). Positive screening (presence of any defined MR, AR, and MS) is followed by confirmatory echocardiography.

Consider RHD Echo active case finding (screening) in children aged 5-20 years living in endemic regions (class 2A) and in first degree relatives of index cases (class 2A), and pregnant women or young adults aged 21-39 years (class 2B) by confirmatory criteria not screening criteria.

MR on screening (all criteria met)	AR on screening (all criteria met)
1. Seen in at least 1 view. 2. Seen for at least 2 consecutive frames. 3. Minimum Jet length ≥ 2 cm if BW ≥ 30 kg or ≥ 10 years or ≥ 1.5 cm if BW < 30 kg).	1. Seen in at least 1 view. 2. Seen for at least 2 consecutive frames. 3. Any AR.
MS: restricted leaflet motion with reduced screening opening	

Confirmatory criteria:

Designed for experts to confirm a diagnosis of RHD with standard ECHO machine

Pathological MR (all 4 criteria met)	Pathological AR (all 4 criteria met)
Doppler features	
4. Seen in at least 2 views. 5. Jet length ≥ 2 cm in at least 1 view (≥ 1.5 cm if BW < 30 kg). 6. Peak velocity > 3 m/s. 7. Pan-systolic in at least 1 envelope.	1. Seen in at least 2 views. 2. Jet length ≥ 1 cm in at least 1 view. 3. Peak velocity > 3 m/s. 4. Pan-diastolic in at least 1 envelope.
Morphological features	
• **Excessive leaflet motion** (tip of AML) during systole with abnormal coaptation (chordal elongation). • **Restricted leaflets motion** (subchordal thickening) • **Leaflets thickening**/nodularity or beading (≥ 3 mm if < 20 years and ≥ 5 mm if > 40 years and ≥ 4 if 20-40 years of age); during diastole at full excursion at the thickest portion. • **Chordal thickening** and fusion. **In advanced cases:** Leaflets calcification, diastolic doming on AML	Focal or irregular leaflets thickening Coaptation defect Leaflets prolapse Restricted leaflets mobility. **Differential diagnosis**: physiological (trivial) regurgitation (not fulfill above criteria), myxomatous mitral valve, mitral valve prolapse, Barlow syndrome, congenital anomalies (parachute mitral valve, cleft MV, double orifice MV & fibroelastoma).
• Some morphological features of RHD take time to develop but may be present in ARF as acute on chronic presentation. • On occasion, valves may appear normal morphologically on echo while Doppler shows regurgitation.	

2012 WHF criteria for echocardiographic diagnosis of RHD

These criteria are widely accepted as the reference standard for diagnosis of RHD in absence of history of acute rheumatic fever.

Definite RHD (one of the following):

1. Pathological MR and at least two morphological features of RHD of the MV.
2. Pathological AR and at least two morphological features of RHD of the AV (< 35 year of age).
3. MS mean gradient ≥ 4 mmHg (exclude other causes of MS).
4. Borderline disease of both the AV & MV (combined borderline valves).
5. If age> 20 year, pathological AR and at least two morphological features of RHD of the MR.

Borderline RHD (one of the following), applicable only for individuals aged < 20 years:

1. At least two morphological features of RHD of the MV without MR or MS.
2. Pathological MR.
3. Pathological AR.

These mentioned terms (definite, borderline and latent) are no longer recommended by the latest 2023 WHF guidelines and replaced by a new classification system that include ECHO criteria and care recommendations to identify the risk of progression (in this system, nearly but not precisely the term "borderline" is replaced by the term "stage A RHD").

Stage A RHD as in 2023 WFH guidelines requires echo features of mild MR or mild AR without morphological features

Latent RHD: Valvular changes consistent with RHD in individual with no history of ARF.

Normal echocardiographic findings (all of the following):

1. Physiological MR (doesn't met pathological MR).
2. Physiological AR (doesn't met pathological AR).
3. Isolated morphological feature of RHD of the MV (for example: valvular thickening).
4. Isolated morphological feature of RHD of the AV (for example: valvular thickening).

Trivial or physiological valve regurgitation or isolated morphological changes should be considered normal or physiological.

RHD stages according to WHF 2023 guidelines

Stage	Echo features	Risk of progression	Care
Stage A (applicable only for children aged ≤20 years)	Mild MR or mild AR without morphological features	Might be at risk of VHD	SAP for 1-2 years then re-view
Stage B (mild RHD)	Mild MR or mild AR plus 2 morphological features (if > 20 years) or 1 feature (if < 20 years) or both mild MR and AR	At moderate or high risk of progression to VHD and at risk of developing symptoms	SAP and other therapies according to local guidelines
Stage C (advanced RHD at risk)	Moderate or severe valve regurgitation, any MS or AS or PH or decreased LVEF.	At high risk of developing complications	SAP and other therapies according to local guidelines
Stage D (advanced RHD with complications)	Moderate or severe valve regurgitation, any MS or AS or PH or decreased LVEF.	Established clinical complications	SAP and other therapies according to local guidelines

Finally, we have two problems still unresolved!

- **Problem of diagnosis:** we don't have a diagnostic tool, research of a diagnostic biomarker is ongoing.
- **Problem of prevention**: the ideal tool is the development of a vaccine for GAS which is under investigation.

References

- 2022 Australian guidelines for ARF and RHD (V 3.2).
- 2014 New Zealand guidelines for rheumatic fever; diagnosis, management and secondary prevention of ARF and RHD
- Prevention of RF, diagnosis and treatment of acute strept pharyngitis (a scientific statement from the AHA)
- Contemporary diagnosis and management of RHD (AHA 2020).
- Revision of the Jones Criteria for diagnosis of ARF in the era of Doppler echo a scientific statement form AHA 2015.
- World Heart Federation criteria for echocardiographic diagnosis of rheumatic heart disease- an evidence based guideline, 2012.
- World Heart Federation guidelines for the echocardiographic diagnosis of rheumatic heart disease, 2023.
- Handbook on prevention and control of rheumatic fever and rheumatic heart disease, ministry of health and family Welfare, government of India, 2015.
- Uptodate.com; management of RHD.